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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/180,269	07/08/1999	KATHRYN LINDSAY BALL	CCI-007US	6599

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EXAMINER
MURPHY, JOSEPH F

ART UNIT	PAPER NUMBER
1646	24

DATE MAILED: 09/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/180,269	BALL ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-12,17,44-47 and 51-59* is/are pending in the application.

4a) Of the above claim(s) *3-5,7 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 6, 8, 10-12, 17, 44-47, 51-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Formal Matters

Claims 2-9, 44, 45 and 51-56 were amended and new claims 57-59 were added in Paper No. 22, 4/22/2003. Claims 2-12, 17, 44-47, 51-59 are pending. The requirement for election of species has been withdrawn, and claims 3-5, 7, 9 have been rejoined. Claims 2-12, 17, 44-47, 51-59 are under consideration.

Response to Amendment and Arguments

Applicant's arguments filed in Paper No. 22, 4/22/2003 have been fully considered but they are persuasive in part.

The objection to claims 2, 44, 45, 57-59 has been withdrawn.

The rejection of claims 10-11, 17, 46, 47 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, has been withdrawn.

Remaining issues are set forth below.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 3, 4, 6, 10-12, 17, 44-47, 51-56 stand rejected, and new claims 57-59 are rejected, under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound which decreases binding between p21 and cyclin D1, wherein the p21 fragment or derivative comprises SEQ ID NO: 2, 10, 28, 11 and 23, does not reasonably provide enablement for a method for identifying a compound which decreases binding between a derivative or analogue of p21 comprising SEQ ID NO: 4, 14 or xyLzF and a derivative of cyclin D1 does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, for reasons of record set forth in Paper No. 22, 4/22/2003.

The rejection of record set forth that claims 2, 3, 4, 6, 10-12, 17, 44-47, 51-59 are overly broad in the recitation of "derivative" and "fragment "since insufficient guidance is provided as to which of the myriad of polypeptide species encompassed by the claim will retain the characteristics of p21 or cyclin D1. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of p21 or cyclin D1. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990) teaches that a single Glu to

Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

Since the claims encompass p21 and cyclin D1 fragments or derivatives, and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to practice the claimed method. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Applicant argues that the claims as amended recites specific sequences or motifs that are shown in the specification to bind either p21 or Cdk4 and are thus enabled. Applicant further argues that the Specification demonstrates the critical residues that are necessary to provide the claimed technical effect, and that thus it would not require one of skill in the art to predict which p21 fragments or derivatives would interact with cyclin D1. While this is found persuasive with respect to fragments of p21 comprising SEQ ID NO: 2, 10, 28, 11 and 23, the specification discloses that the essential residues for activity are RRLIF. Insofar as the claims are drawn to methods of identifying compounds which modulate binding between p21 and cyclin D1 or cdk4, wherein the derivative or analogue of p21 comprises SEQ ID NO: 4, 14 or xyLzF, the claims are not enabled because as the specification discloses these sequences do not comprise the residues essential for the peptides to be active. Since these peptides do not comprise the essential residues necessary for function, it would require undue experimentation for one of skill in the art to practice the claimed method, since the

skilled artisan would have to first make polypeptide variants of p21 or cyclin D1, and then determine whether the peptides would function in the claimed method. Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass methods using polypeptide derivative and fragments for which the skilled artisan would have to test for function. Since the claims do not enable one of skill in the art to make and use polypeptide fragments and derivatives, and since detailed information regarding the structural and functional requirements of the polypeptide fragments and derivatives are lacking, it is unpredictable as to which fragments and derivatives, if any, meet the limitations of the claims.

Claims 2, 3, 4, 6, 10-12, 17, 44-47, 51-56 stand rejected, and new claims 57-59 are rejected, under 35 U.S.C. 112, first paragraph, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in Paper No. 22, 4/22/2003. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The rejection of record set forth that these are genus claims. Because of the use of the terms fragments, derivatives or analogues in the claims, the claims encompass proteins having one or more amino acid substitutions, deletions, insertions and/or additions made to cyclin D1 or

p21. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to cyclin D1 or p21. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the specification states that these types of changes are routinely done in the art, the specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, cyclin D1 or p21 alone are insufficient to describe the genus. Applicant argues that the amended claims include distinguishing attributes of the members of the genus, and that the amended claims recite the limits of the identity the derivatives and fragments of p21 and cyclin D1 must possess. While this is found persuasive with respect to fragments of p21 comprises SEQ ID NO: 2, 10, 28, 11 and 23, the specification discloses that the essential residues for activity are RRLIF. Insofar as the claims are drawn to methods of identifying compounds which modulate binding between p21 and cyclin D1 or cdk4, wherein the derivative or analogue of p21 comprising SEQ ID NO: 4, 14 or xyLzF, the claims lack description because these peptides do not comprise the residues essential for activity. The written description requirement for a claimed genus may be satisfied through sufficient description of a

representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification sets forth the essential residues necessary for function, and the derivative or analogue of p21 comprising SEQ ID NO: 4, 14 or xyLzF does not comprise these essential residues. Since the specification does not sufficiently disclose the correlation between peptides which do not comprise the essential RRLIF sequence, and the function of interacting or binding cyclin D1 or cdk4, therefore the claims lack written description.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 6, 8, 10-12, 17, 44-47, 51-56 stand rejected, claims 3-5, 7, 9, as well as new claims 57-59 are rejected, under 35 U.S.C. 103(a) as being unpatentable over WO 94/09135 (Beach et al.) in view of Xiong et al. (1993), for reasons of record set forth in Paper No. 21, 10/22/2002.

Beach et al. discloses the association between cyclin D, p21 and cdk 4, and its disruption upon introduction of SV40 tumor virus or its gene product (page 3, lines 35-36). Beach et al. discloses that inhibitors of p21 can be introduced into cells and interfere with p21 binding to complex members (i.e. including cyclin D) (page 4, line 27-28). Beach et al. also discloses that drugs which alter p21 function can be used to inhibit or enhance cell division (page 25, lines 22-23). Beach discloses a method of screening compounds for their ability to inhibit or suppress the transformation of a cell, which may include prevention of formation of complexes including cyclin D, p21 and CDK (page 24, line 12 to page 25, line 9). Beach et al. teaches that it is possible to selectively decrease mitotic capability of cells by the use of an agent, which is designed to interfere with the activity of a complex comprising a particular D type cyclin and CDK. Beach et al. teaches screening of a compound which selectively inhibits interaction of a D-type cyclin with CDK4 (page 25, lines 16-20). Beach discloses that drugs which alter p21 function can be used to inhibit or enhance cell division (page 25, lines 22-23), and that these drugs can be small peptides that mimic the complex constituent in terms of binding but which lacks its active regions (page 25, lines 25-26).

Beach et al. does not list the sequence of p21, hence the Xiong et al. reference is cited to exemplify that the sequence of p21 comprises the claimed KRRLIFSK sequence (see Sequence Comparison A, attached). Therefore, it would have been obvious to one of skill in the art at the

time the invention was made to practice the method disclosed in Beach et al. to screen for a compound which modulates the interaction of p21 and cyclin D and cdk 4. The motivation is provided in Beach et al. which discloses that p21 is known to associate with cyclin kinases only in normal, untransformed cells, and thus offers specificity in modulating cell division, for example the ability to selectively alter cell division in particular cell types or at a particular point in the cell cycle (page 4, lines 7-15). The expectation of success is provided by Beach et al., which teaches that agents which selectively inhibit cyclin D1 are expected to be particularly useful (page 25, lines 1-6).

Applicant argues that the Beach reference does not provide an enabling disclosure because it does not disclose the association between cyclin D1, p21 and cdk4. Applicant further argues that there is no teaching in the Beach reference that teaches that inhibitors of p21 can interfere with p21 interaction with cyclin D1 or cdk4. However, the Beach reference clearly teaches methods of compound screening (page 24, line 10 to page 25 line 6), and also teaches the interaction between cyclin D, p21 and cdk 4, and its disruption upon introduction of SV40 tumor virus or its gene product (page 3, lines 35-36). Applicant further argues that the Beach reference only teaches that the reference only teaches the measurement of the disruption of the interaction by measuring cell transformation, and not measuring the interaction. However, the cell transformation is the measurement of the interaction of the molecules. The instant claims do not set forth a specific methodology which must be used to measure the interaction of the proteins, and a functional assay as set forth in the Beach reference is capable of determining the interaction between the molecules in the presence of a test compound. Applicant further argues that the Beach reference does not teach the specific details of the interaction between p21 and

constituents in the complex. However, as set forth supra, Beach teaches the cyclin D, p21 and cdk 4, and a method of measuring the effect of a test compound by measuring cell transformation. Thus, the Beach reference has an enabling disclosure for one of skill in the art to practice a method to screen for a compound which modulates the interaction of p21 and cyclin D and cdk 4.

Applicant further argues that the Examiner has used impermissible hindsight to reconstruct to use a protein fragment of the KRRLIFSK sequences. However, the claims are directed to methods using fragments comprising this sequence, not the use of the sequence alone, and thus the Xiong reference was cited to show it is an expected property of the p21 protein to comprise the KRRLIFSK sequence. Thus, there was no impermissible hindsight reasoning used.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
September 22, 2003

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